IN THE SPECIFICATION:

Page 3, paragraph 0008 (in the published version) is corrected to read "cite" rather than "site". Page 5, paragraph 0012, is amended to remove control marks, and to correct the patent number of the reference being discussed from 5,547,147 to 5,457,147). Paragraphs 0019, 0020 0021 and 0022 (pages 9 - 11) are amended to correct the reference (from '062 to '662). Page 19, paragraph 0045, is corrected so that "noot" is replaced by "not".

In addition, on p. 12, second paragraph, 3rd line (para. 0044 of US published) please replace "lease" with "least" and "occurr" with "occur". On p. 15, line 1 (Para. 0056 3rd from last line) please replace "my" with "by". In para 18, correct "polyiscyanate" to "polyisocyanate"; in para. 0026 please correct "fomulate" to "formulate"; in para 0049 please replace "trimethyloethane" with "trimethylolethane"; in para. 0065 please replace " polypropylene/polyethyle- ne" with " polypropylene/polyethylene", and in para 0070 please correct " polypro-pylene/polyethylene" to " polypropylene/polyethylene".

The corrected paragraphs are presented below. It is believed that no new matter is introduced in the course of these corrections.

[0008] The examples of U.S. Pat. No. 4,806,614 cite p-phenylene diisocyanate, which is not reactive enough to form strong tissue bonds. Those with TDI (Toluene Diisocyanate) do not have the proper PEO/PPO (polyethylene oxide/polypropylene oxide) ratio to form hydrogels. The examples given and the text illustrate that a hydrogel formation was not a goal of U.S. Pat. No. 4,806,614. U.S. Pat. No. 4,806,614 does not teach formation of a hydrogel with 30-90% water. Devices of the type given in U.S. Pat. No. 4,806,614 will take up about 10% water.

[0012] U.S. Pat. No. 5,457,147 (McGrath et al.) describes a process for the formation of poly(secondary amine) comprising units of Structure 6 wherein P_1 represents the repeating unit of a polymer containing olefinic unsaturation which has been hydroformylated and reductively aminated. P_2 represents the repeating unit of the same polymer containing olefinic unsaturation having reactive carbon-carbon double bonds. R

is selected from the group consisting of aliphatic, aromatic, cycloaliphatic, substituted aliphatic, aromatic and cycloaliphatic groups and combinations thereof, and the ratio of P_1 to P_2 is about 1:99 to about 90:10. The U.S. Pat. No. 5,457,147 refers to amines of a particular structure, and more generally to processes for creating such amines. This patent does not teach or relate to tissue bonds. The amines formed by the reaction of the adhesive of the present invention with tissue which forms the bond, is not taught by the '147 patent since the tissue portion of the '147 patent is not a repeating unit polymer containing olefinic unsaturation. Furthermore, the amines discussed in the '147 patent require the metal catalysts primarily concerned with controlling functional density. The hydroformylation reaction is conducted under a monoxide/hydrogen atmosphere at a high pressure. The processes are not useful in the formation of tissue bonds.

[0018] Furthermore, claim 1 of the '662 patent is very specific about the type of isocyanate to be used although the text is more general. Claim 1 is not particular about the isocyanate being poly-functional, although the text discusses difunctional alternatives. The absence of a poly-functional specification and the absence of a catalytic formation of amine by reaction of free ~~polyisocyanate~~ polyisocyanate with water leads to the conclusion that claim 1 of the '662 patent does not relate to tissue adhesives, except insofar as being a component. Such a composition would have minimal tissue bonding capability.

[0019] The type of isocyanate specified in the '662 patent will likely require a catalyst to be effective as a tissue adhesive. For example, in the text it states, "Cross-linking is normally performed by exposing the terminated polymer to water in the presence of a catalyst, such as a tertiary amine". It does not teach in the text nor does it specify in the claims the use of an excess for polyisocyanate and its interaction with body fluids to produce the necessary amine. It is not specified in the text or in the claims what fraction of the star molecule's arms are terminated. This specification is critical to ensure propagation of tissue interpenetrating structures, and in the absence of further teaching would favor self-polymerization over crosslinking to tissue structures.

[0020] There is some question as to whether the composition of claim 1 is bioabsorbable since the minor component is bioabsorbable, and the polyfunctional aspects of the

alkylene oxide units may produce sufficient cross linking to prevent dissolution of the cured composition. The text of the '662 patent teaches away from surgical adhesives stating, "It has been discovered that novel polymers in accordance with this disclosure can serve as a substrate for cell growth. Specifically, star polymers terminated with lysine diisocyanate, with or without an induced charge, can be used as a cell growth substrate." The text further teaches away from a surgical adhesive by citing applications of the composition recited in claim 1 that are nonfunctional with respect to the isocyanate, ". . . one or more medico-surgically useful substances, e.g., those which accelerate or beneficially modify the healing process when particles are applied to a surgical repair, can be incorporated into surgical devices made from materials described herein . . . . " The text thus strongly suggests that the composition recited is to be used as a delivery device for therapeutics in its cured or cross-linked state, not as a tissue adhesive. The text also does not link isocyanate reactivity to the composition's ability to deliver therapeutics.

[0021] All of the examples use a catalyst, Sn(Oct) which is toxic and not acceptable for use in the manufacture of medical devices. The present invention achieves its composition without the use of catalysts and specifically teaches away from their use. Furthermore, the composition of the '662 patent could not be manufactured without the use of these catalysts since the arms of the star molecule would likely sterically hinder arm termination by isocyanate.

[0022] Finally, the abstract and text of the '662 patent suggests the composition taught is fully crosslinked before its use in the body. For example, "The star polymers can be terminated with isocyanate, mixed with a filler and/or cross-linked." It appears that the reference of its teachings as a surgical adhesive is restricted to those substances that are tacky or mechanically adhesive and non-functional with respect to the isocyanate.

[0026] It is another object of the present invention to achieve a catalytic amine by providing in the 1-part ~~fomulation~~ formulation an excess of free polyisocyanate that is transformed to the amine by body fluids.

[0044] The present invention also comprises a method of establishing an organic hydrogel bond at a situs of living tissue comprising the steps of: pre-treating disparate portions of the living tissue with free polyisocyanate, body derived fluids, at ~~lease~~ least one NCO-terminated hydrophilic polyol, derived from an organic polyisocyanate, and bonding or sealing the living tissue. The steps preferably ~~occurr~~ occur as a result of contact between present invention and living tissue.

[0045] The present invention relates to a 1-part surgical adhesive wherein covalent bonds are formed with body tissue and a hydrogel is formed of body fluids. However, the vast majority of NCO-terminated hydrophilic urethane prepolymers do not form such hydrogels. Urethane prepolymers are deemed hydrophilic if they incorporate in the urethane structure between 2 and 10% water. Such prepolymers are not effective as surgical adhesives since they are not hydrophilic enough and do not form hydrogels. Such prepolymers, when placed in an environment where the water exceeds 10% of the prepolymer volume polymerize internally without linking to tissue or fail to form a solid.

[0049] Tri-functional PE/PO polyols can be prepared by reacting PE/PO diols of between 800 and 5,000 MW with a triol. There are many suitable triols: triethanolamine, trimethylolpropane, ~~trimethyloethane~~ trimethylolethane and glycerol.

[0056] In the application of the adhesive of the present invention to body tissue, the adhesive may be applied conventionally with a standard syringe fitted with a suitable gauge needle. The syringe can be heated in a warm water bath to further decrease adhesive viscosity. Hemostasis can be achieved by applying the adhesive to a suitable substrate such as meshes made of polyester, polypropylene, oxidized cellulose, collagen, or like materials. Cured sheets of the adhesive can be bonded to tissue by applying a thin layer of uncured adhesive thereon. Various grafts and tissue anastomoses can be sealed and/or joined using the adhesive. The adhesive can coat standard sutured anastomoses rendering them hemostatic or the adhesive can be used to buttress sutures or mechanical applier devices such as staples. The adhesive bonds to any material containing water, and will mechanically bond porous or woven materials. Applicable tissues include blood

vessels, lung, heart, esophagus, stomach, and skin. The adhesive can also be used to augment tissue ~~my~~ by injection into tissue. The adhesive can be used to deliver therapeutics such as water soluble drugs, radiation sources, and chemo therapies.

[0065] The invention thus comprises a biocompatible tissue-bonding adhesive composition comprising: a polyol of functionality N, wherein the polyol being terminated with at least one polyisocyanate in solution with at least (N-1)% of said solution comprising free polyisocyanate. N may be in the range 1.5-8. The polyol may be a branched ~~polypropylene/polyethyle- ne~~ polypropylene/polyethylene oxide copolymer. The polypropylene/polyethylene oxide copolymer contains polypropylene oxide in a range of about 10% and 30%. The polypropylene/polyethylene oxide copolymer may contain no more than 10% polypropylene oxide. The polyisocyanate may be comprised of a 80:20 mixture of 2,4-toluene diisocyanate and 2,6-toluene diisocyanate. The polyisocyanate may consist of 2,6-toluene diisocyanate only. The polyisocyanate may consist of isophorone diisocyanate. The polyisocyanate may consist of an 80:20 mixture of 2,4-toluene diisocyanate and 2,6-toluene diisocyanate and 3% of the composition is free polyisocyanate. The polyisocyanate may consist of isophorone diisocyanate and about 1.5% of the composition consists of free polyisocyanate. The composition may be comprised of two polyisocyanates and wherein one of the polyisocyanates comprises a free isocyanate B as an aromatic polyisocyanate and the other of the polyisocyanates comprises an aliphatic isocyanate A which is used to endcap said copolymer. The free isocyanate B may convert to an amine faster than the isocyanate A. The free isocyanate B may be more reactive with nitrogenous substances than the isocyanate A. The free isocyanate B may be of lower viscosity than the isocyanate A.

[0070] The invention may also include a method for covalent bonding of tissue, which comprises: applying thereto a 1-part surgical adhesive consisting of two NCO-terminated branched polypropylene/polyethylene oxide copolymers, wherein copolymer A is at most 10% polypropylene oxide and copolymer B is between 10% and 30% polypropylene oxide, derived from an organic polyisocyanate and at least 1% unreacted polyisocyanate

wherein the polymerization proceeds by the following time-ordered steps: the free polyisocyanate bonds to tissue, the free polyisocyanate converts to a polyamine and links both polypropylene/polyethylene oxide copolymers to the tissue bonded polyisocyanate, the free polyisocyanate converts to polyamine and links the branched ~~polypro-pylene/polyethylene~~ polypropylene/polyethylene oxide copolymers to the other same polymers, and polymerized copolymer A swells within the formed polymer matrix and causes degradation of the formed matrix.